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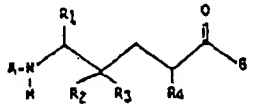
(54) **Novel peptides, their preparation & use**

(57) Compounds of formula I



[wherein R_1 and R_4 are hydrophilic or hydrophobic side chains; R_3 is hydrogen and R_2 is amino or hydroxy or R_3 and R_2 together are oxo; and A and B have the significances given in claim 1] processes for the production thereof, and their use as a *renin inhibitor* (e.g. in the treatment of *hypertension* and *cardiac insufficiency*) and for the *treatment of diseases caused by retroviruses*.

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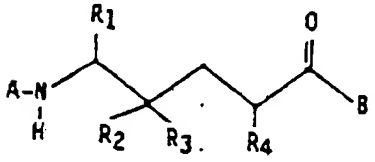
NOVEL PEPTIDES, THEIR PREPARATION AND USE

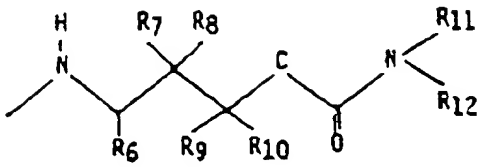
The present invention relates to novel renin-inhibitors, their preparation and use as well as pharmaceutical compositions containing them.

The invention provides a compound of formula I,



I

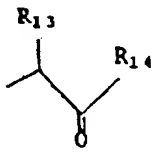
B signifies either a group of formula,



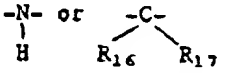
wherein R_6 has the same significance as R_1 and R_7 and R_8 have the same significances as R_2 and R_3,

R_9 and R_{10}, independently of one another, respectively signify hydrogen or fluorine,

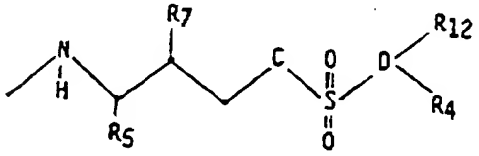
R_{11} and R_{12} are the same or different and respectively signify hydrogen, a straight-chain or branched (C_{1-5})alkyl radical, a (C_{6-10})aryl-(C_{1-5})alkyl or a heteroaryl-(C_{1-5})alkyl radical, in which the heteroaryl moiety is 5- or 6-membered and contains one or two nitrogen atoms, oxygen or sulphur atoms or one nitrogen atom and one oxygen atom and/or one sulphur atom,

or they signify a group of formula 

wherein R_{13} signifies a straight-chain or branched (C_{1-5})alkyl radical or a straight-chain or branched (C_{1-5})hydroxyalkyl radical, R_{14} signifies a hydroxyl radical, a straight-chain or branched (C_{1-5})alkoxy group, an amino or a (C_{1-5})alkylamino group, whereby the alkyl radical is straight-chain or branched, an aminomethylpyridyl group or a benzyl group,

C signifies a bond, or denotes -O-, -N(H)- or  wherein R_{16} and R_{17}, independently of one another, denote hydrogen or fluorine, or they have the significance given for R_4, or

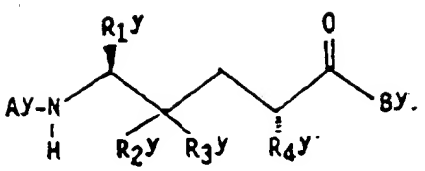
B signifies a group of formula,



wherein R_4, R_5, R_7 and R_{12} possess the above-mentioned significances and D is -N- or -CH-.

Asymmetrically substituted C-atoms may have R- or S-configuration. The configurations given in the following formula I^y are preferred.

Preferred compounds of formula I possess formula I^y,



I^y

wherein

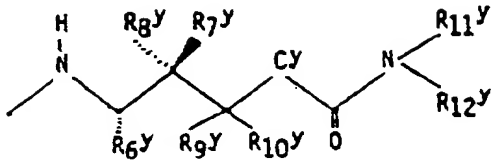
A^y signifies benzyloxycarbonyl, tert. butoxycarbonyl, pivaloyl, benzoyl or adamantylcarbonyl,

R_1^y signifies cyclohexylmethyl, phenylmethyl, isobutyl and

R_2^y and R_3^y together signify the oxo group, or R_2^y signifies hydrogen and R_3^y signifies hydroxyl,

R_4^y signifies phenylmethyl, n-butyl, isobutyl, isopropyl, pyridylmethyl, 2-butenyl or methylthiomethyl,

B^Y signifies a group of formula,

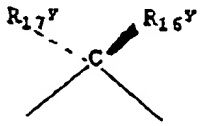


wherein R_6^Y is isobutyl, benzyl or cyclohexylmethyl, and either

R_7^Y signifies a hydroxyl radical and R_8^Y signifies hydrogen, if R_9^Y and R_{10}^Y respectively denote hydrogen, or

R_7^Y and R_8^Y together signify the oxo group, if R_9^Y and R_{10}^Y respectively denote fluorine.

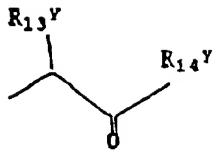
C^Y signifies a bond or a group of formula



wherein R_{16}^Y and R_{17}^Y are fluorine, or R_{16}^Y has the significance of R_4^Y and R_{17}^Y signifies hydrogen,

R_{11}^Y signifies hydrogen or methyl,

R_{12}^Y signifies hydrogen, methyl, i-propyl, i-butyl, 2-butyl or a group of formula



wherein R_{13}^Y is i-butyl and R_{14}^Y is aminomethylpyridyl.

In formula I, R_5 when it is a straight-chain or branched alkyl with 1 to 10 carbon atoms signifies in particular methyl, ethyl, propyl, isopropyl, butyl, tert. butyl, 2,2-dimethylethyl, pentyl, hexyl etc., especially methyl, tert. butyl and 2,2-dimethylethyl, and if it is substituted by aryloxy, it is especially phenoxymethyl or 1- or 2-naphthyloxymethyl, preferably 1-naphthyloxymethyl, when it is cycloalkyl with 3-10 carbon atoms, it is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or adamantyl when it is (C_{3-10})cycloalkyl-(C_{1-5})alkyl, cycloalkyl may have the above significances and the residue is in particular 2-cyclohexylethyl- or 2-(1-adamantyl)ethyl, when it is (C_{6-10})-aryl it is especially phenyl or 1- or 2-naphthyl, preferably 1-naphthyl, when it is a heteroaryl radical it signifies in particular pyridyl, thienyl or furyl, when it is a heteroarylalkyl radical the heteroaryl moiety and the alkyl moiety preferably have the above-mentioned significances, when it is a straight--chain or branched alkoxy radical it signifies in particular ethoxy or tert. butoxy, and when it is (C_{6-10})aryl-(C_{1-5})-alkoxy, it has in particular the significances given for aryl and alkyl, and is preferably benzyloxy.

In the group $R_{15}O(CH_2CH_2O)_n(CH_2)_m-$, R_{15} preferably signifies methyl, n is preferably a whole number from 4 to 12, especially 7, and m is preferably 1.

The hydrophobic side chain in the definition of R_1 and R_4 may be for example a n-butyl, isobutyl, benzyl, 2-butenyl, 2-methylthioethyl or cyclohexylmethyl radical, a hydrophilic side chain in the definition of R_1 and R_4 may be for example a 4-imidazolylmethyl, pyridylmethyl or hydroxylalkyl radical.

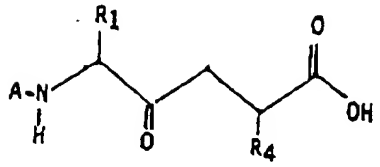
When R_{11} and R_{12} denote a (C_{6-10})aryl-(C_{1-5})-alkyl radical, they preferably signify a phenyl-(C_{1-5})-alkyl, especially a benzyl radical, when they denote a heteroarylalkyl radical, the heteroaryl moiety signifies in particular a pyridyl, thienyl or furyl radical and alkyl denotes the above-mentioned radicals.

When R_{11} and R_{12} denote (C_{1-4})alkyl, alkyl has the significances given above in connection with R_5, restricted to 1-5 carbon atoms.

When R_{13} denotes a (C_{1-5})alkyl radical, alkyl signifies the above-mentioned radicals, but especially isopropyl, n-butyl, isobutyl and 2-methylbutyl. Hydroxyalkyl preferably signifies hydroxymethyl or hydroxyethyl. When R_{14} signifies aminomethylpyridyl, it is preferably aminomethyl-2-pyridyl.

The preparation of compounds of formula I is characterised in that

a) a compound of formula II,



II

wherein A, R_1 and R_4 are defined above
is reacted with a compound of formula H-B.
wherein B is defined above

b) a compound of formula I, in which R_7 = OH and R_8 = H, is oxidised to form a compound of formula I, in which R_7 and R_8 together form an oxo group,

c) a compound of formula I, in which R_2 and R_3 together form an oxo group, is reduced to form a compound of formula I, in which R_2 = OH and R_3 = H,

d) a multiple bond found in side chains R_4, R_{16} or R_{17} is reduced, or

e) the protecting group is cleaved from a compound of formula I, in which A is t-BOC, and the free amine is acylated again.

The process according to stage a) is preferably carried out such that an acid of formula II is reacted with an amine of formula H-B, using processes which are known in peptide che-

mistry, e.g. in the presence of N,N'-dicyclohexylcarbodiimide (adding 1-hydroxybenzotriazole) in a suitable solvent such as methylene chloride, at temperatures of between 0° and room temperature.

The process according to stage b) is carried out such that an alcohol of formula I is oxidised with $CrO_3.Py_2$ (Collin's reagent) in a solvent such as methylene chloride or DMF, to form the corresponding ketone.

The process according to stage c) is preferably carried out such that a ketone of formula I is reduced with $NaBH_4$ in a solvent such as methanol, to form the corresponding alcohol.

The process according to stage d) conveniently takes place using palladium (10% on active charcoal) as a catalyst in a solvent such as ethanol, at a hydrogen pressure of 1 to 5 atm, at temperatures of room temperature to 60°.

The reaction according to stage e) of the process is preferably effected such that the t-BOC group is cleaved in the presence of trifluoroacetic acid at temperatures of 0 to 5°, and the free amine is acylated with an active acid derivative, e.g. hydroxy-succinimide esters, in a solvent such as methylene chloride.

The starting compounds used in the above processes are either known or may be produced in known manner, for example as described in the following examples.

The compounds of formula I which are produced according to the invention may be isolated and purified in known manner. Racemic and/or diastereoisomeric mixtures may be separated in known manner.

If the compounds of formula I contain acidic or basic groups, these may also optionally form salts, for example metal salts such as sodium salts or acid addition salts such as hydrochlorides.

In the following examples, all temperatures are given in °C and are uncorrected.

The compounds given in abbreviated form in the examples are described fully in claim 3 in the order given in the examples.

In the following examples, the following abbreviations are used:

H-F_2CHaOH	(3R, 4S)-4-amino-5-cyclohexyl-2,2-difluoro-3-hydroxy-valeric acid
H-F_2Cho-OH	(4S)-4-amino-5-cyclohexyl-2,2-difluoro-3-oxo-valeric acid
H-Cha(OH)Ala-OH	(2R, 4S, 5S)-5-amino-6-cyclohexyl-4-hydroxy-2-methyl-caproic acid
H-Cha((OH)Nle-OH	(2R, 4S, 5S)-5-amino-2-butyl-6-cyclohexyl-4-hydroxy-caproic acid
H-Cha(O)Nle-OH	(2R, 5S)-5-amino-2-butyl-6-cyclohexyl-4-oxo-caproic acid
H-Cha(OH)Bly-OH	(2R, 4S, 5S)-5-amino-2-(E-2-butenyl)-6-cyclohexyl-4-hydroxy-caproic acid

H-Cha(O)Bly-OH	(2R, 5S)-5-amino-2-(E-2-butenyl)-6-cyclohexyl-4-oxo-caproic acid
H-Cha(OH)Phe-OH	(2R, 4S, 5S)-5-amino-2-benzyl-6-cyclohexyl-4-hydroxy-caproic acid
H-Cha(O)Phe-OH	(2R, 5S)-5-amino-2-benzyl-6-cyclohexyl-4-oxo-caproic acid
H-Leu(O)leu-OH	(2R, 5S)-5-amino-2-isobutyl-7-methyl-4-oxo-caprylic acid
BOC	tert.-butyloxycarbonyl
Z	benzyloxycarbonyl.
[α]D	is always measured at 20°C.

Example 1: t-BOC-Cha(O)Bly-F_2Cha-NHiBu

140 mg of F_2ChaNHiBu are reacted in 2 ml of tetrahydrofuran with 170 mg of t-BOC-Cha(O)Bly-OH in the presence of 120 mg of hydroxybenzotriazole and 97 mg of N,N'-dicyclohexylcarbodiimide for 2 hours at 0°, then for 24 hours at room temperature. The precipitated dicyclohexylurea is filtered off, and the filtrate is chromatographed on silica gel with ether/hexane 10-50%. $[\alpha]D$ = -7.3° (c = 0.4 in methylene chloride).

Example 2: t-BOC-Cha(O)Bly-F_2Cho-NHiBu

22 mg of the product of example 1 are dissolved in 1.8 ml of methylene chloride and mixed with 84 mg of Collin's reagent ($CrO_3.Py_2$). After 30 mins., ethyl acetate is added, the mixture is filtered over Hyflo (Rfm) and silica gel and the filtrate is lyophilised from benzene. $[\alpha]D$ = +4.6° (c = 0.17 in methylene chloride).

Example 3: t-BOC-Cha(O)Nle-F_2Cha-NHiBu

12 mg of the product of example 1 are dissolved in 1.2 ml of ethanol, and hydrogenated for 4 hours in the presence of 1.4 mg of Pd/C. The catalyst is filtered off and the filtrate is concentrated by evaporation. $[\alpha]D$ = -5.7° (c = 0.14 in methylene chloride).

Example 4: t-BOC-Leu(O)Leu-F_2Cha-Leu-2-picoline

115 mg of F_2Cha-Leu-2-picoline, 78 mg of t-BOC-Leu(O)Leu-OH, 60 mg of hydroxybenzotriazole and 47 mg of N,N'-dicyclohexylcarbodiimide are reacted analogously to example 1. The crude product is chromatographed with ether on silica get. $[\alpha]D$ = +8.0° (c = 0.2 in methylene chloride).

Example 5: t-BOC-Cha(O)Phe-Cha(OH)Phe-NHBu

34 mg of Cha(OH)Phe-NHBu, 40 mg of t-BOC-Cha(O)Phe-OH, 25 mg of hydroxybenzotriazole and 20 mg of N,N'-dicyclohexylcarbodiimide are reacted analogously to example 1. The crude product is chromatographed on silica gel with ether in hexane (40 to 100%). $[\alpha]D = +13.7°$ (c = 0.1 in methylene chloride).

Example 6: t-BOC-Cha(O)Bly-Cha(OH)Bly-NHBu

37 mg of Cha(OH)Bly-NHBu, 40 mg of t-BOC-Cha(O)Bly-OH, 17 mg of hydroxybenzotriazole and 22 mg of N,N'-dicyclohexylcarbodiimide are reacted analogously to example 1. The crude product is chromatographed with ether in hexane (40-100%). $[\alpha]D = -11.4°$ (c = 0.1 in methylene chloride).

Example 7: t-BOC-Cha(O)Nle-Cha(OH)Nle-NHBu

30 mg of the product of example 6 are dissolved in 2 ml of ethanol, and hydrogenated for 3 hours in the presence of 3 mg of Pd/C. $[\alpha]D = -13.0°$ (c = 0.1 in methylene chloride).

Example 8: t-BOC-Cha(OH)Bly-Cha(OH)Bly-NHBu

10 mg of the product of example 6 are dissolved in 0.5 ml of methanol and reacted with 5 mg of sodium borohydride. After 1/2 hour, the solution is diluted with ether, washed with aqueous tartaric acid (2N) solution, the organic phase is dried over magnesium sulphate and concentrated by evaporation. The product is obtained as a diastereoisomeric mixture ca. 2:1.

Example 9: Z-Cha(O)Bly-Cha(OH)Bly-NHBu

30 mg of the product of example 6 are left to stand for 1 hour in a mixture of trifluoroacetic acid and methylene chloride 1:1 (0.5 ml), whereby the protecting group is split off. The mixture is then diluted with methylene chloride, extracted with aqueous soda solution (2N), the organic phase is dried with potassium carbonate, concentrated by evaporation and reacted at 50° with 15 mg of N-(benzyloxycarbonyloxy)-succinimide in 0.5 ml of tetrahydrofuran. The crude product is dissolved in ether, washed with water, dried and concentrated by evaporation. $[\alpha]$ D = -14.6° (c = 0.05 in methylene chloride).

Example 10: t-BOC-Leu(O)Leu-F_2Cho-Leu-2-picoline

65 mg of the product of example 4 are reacted with 150 mg of Collin's reagent analogously to example 2. $[\alpha]$D of the title compound obtained = 16.2° (c = 0.1 in methylene chloride).

Intermediate products:

t-BOC-Cha(O)Bly-OH

293 mg of t-BOC-Cha(OH)Bly-OH are dissolved in 7 ml of dimethylformamide and reacted with 1.54 g of Collin's reagent. The reaction mixture is partitioned between ether and aqueous potassium bisulphate solution, the organic phase is washed with water, dried over magnesium sulphate and concentrated by evaporation.

Example 11: BOC-Cha(O)Bly-Cha(OH)Bly-Leu-α-picoline

66 mg of H-Cha(OH)Bly-Leu-α-picoline, 52 mg BOC-Cha(O)Bly-OH, 20 mg hydroxybenzotriazole and 30 mg N,N'-dicyclohexylcarbodiimide are reacted analogously to example 1. The crude product is chromatographed with 3% methanol in methylene/chloride. [α]D = -26.0° (c = 0.1 in methylene chloride).

Example 12: BOC-Cha(O)Bly-Cha(OH)Ala-NHBu

0.84 g H-Cha(OH)Ala-NHBu, 1.09 g BOC-Cha(O)Bly-OH, 0.5 g hydroxybenzotriazol and 0.6 g N,N'-dicyclohexylcarbodiimide are reacted analogously to example 1. The crude product is chromatographed on silica gel with ether/methylene chloride (20 to 60%). [α]D = -16.9° (c = 0.2 in methylene chloride).

The compounds of Formula I exhibit pharmacological activity and are, therefore, useful as pharmaceuticals.

They are inhibitors of renin activity, e.g. on human tetradecapeptide substrate at a concentration of 10^{-5} M to 10^{-11} M they inhibit the enzyme activity of pure human renin by 50 % according to the method of F. Cumin et al. (Bioch. Biophys. Acta) 913, 10 to 19 (1987) or in a renin binding assay.

In the antibody-trapping method of K. Poulsen and J. Jrgensen (J. Clin. Endocrin. Metab. 39, [1974] 816-825), they inhibit human plasma renin activity at a concentration of 10^{-5} M to 10^{-11} M.

The compounds according to the invention are therefore useful for the prophylaxis and treatment of conditions which are characterised by enzymatic malfunction and for which an inhibition of enzymatic activity is indicated.

As renin inhibitors they are suitable e.g. for use in the prophylaxis and treatment of hypertension and cardiac insufficiency ("congestive heart failure").

The compounds which are preferred for the prophylaxis and treatment of hypertension and cardiac insufficiency are the title compounds of examples 1 and 4 to 12, especially examples 5, 6 and 8 to 10, particulary examples 5, 6, 8 and 10, most preferred the compound of example 8.

The title compound of example 8 is the preferred compound for the renin inhibition, it has for example been determined in the antibody trapping test having the lovest inhibiting concentration 0,15 nM/l, the highest inhibiting concentration 15 nM/l, IC_{50}=1,5 nM/l, it is therefore indicated that the compound of example 8 may be administered to larger mammals such as humans at daily dosage from 1 mg to 10 mg.

The compounds according to the invention exhibit also an anti-retroviral activity and are therefore useful for the treatment of diseases caused by retroviruses including HTLV-I and -III. This activity can be demonstrated in the FeLV cat model [Cerny + Essex, CRC press in 1979, pp. 233-256; Cockerell et al. J. Natl. Cancer Inst. 57, 1095-1099 (1976); Cotter et al. J. Am. Vet. med. Assoc. 166, 449-453 (1975); Essex et al. Science 190, 790-792 (1975)] - a disease model for human AIDS.

It has been reported e.g. (25th ICAAC in Minneapolis, Sept. 30th - Oct. 2nd) that with a 30 mg treatment of 3'-azido-3'-deoxy-thymidine over 14 days a reduction of FeLV-titres by a factor of 10 could be shown, but no cure was achieved. On administration of the compounds of the invention eradication of the virus can be observed. Dosage ranges for the anti-retro-viral activity are

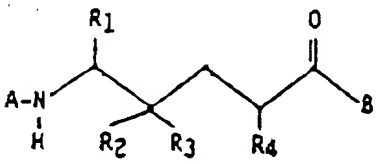
also those conventionally employed and lie e.g. in the range of 5-20 mg/kg/day.

For above indications, the dosage to be administered depends on the compound respectively used, the type of administration and the desired treatment. In general, satisfactory results are obtained if the compounds are administered in a daily dosage of 0.02 mg/kg to ca. 20 mg/kg animal body weight. For larger mammals, for example humans an indicated daily dosage is from about 1 mg to about 500 mg, conveniently administered e.g. orally in doses of 0.25 mg to ca. 500 mg up to 4 times daily e.g. in divided form.

The compounds according to the invention may be administered in free form, or if acidic or basic groups are present, in pharmacologically acceptable salt form. Such salt forms have the same order of activity as the free forms and can be produced in known manner. The present invention similarly relates to pharmaceutical preparations containing a compound according to the invention in free form or in pharmaceutically acceptable salt form, optionally together with pharmaceutically adjuvants and/or carrier substances. Such pharmaceutical preparations may be formulated for use in enteral, preferably oral administration, e.g. at tablets, or for use in parenteral administration, e.g. as injectable solutions or suspensions.

WHAT WE CLAIM IS:

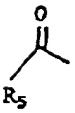
1. A compound of formula I,



I

wherein

A is a N-protected amino acid radical,

or it signifies an acyl group of formula 

wherein R_5 denotes a straight-chain or branched (C_{1-10})alkyl radical which may be optionally substituted by (C_{1-5})alkoxy or (C_{6-10})aryloxy; a (C_{3-10})cycloalkyl radical, a (C_{3-10})cycloalkyl-(C_{1-5})alkyl radical, a (C_{6-10})aryl radical, a 5- or 6-membered heteroaryl radical containing one or two nitrogen atoms, oxygen or sulphur atoms or one nitrogen atom and one oxygen atom and/or one sulphur atom, or a heteroaryl-(C_{1-5})alkyl radical in which the heteroaryl moiety is 5- or 6-membered and contains one or two nitrogen atoms, oxygen or sulphur atoms or one nitrogen atom and one oxygen atom and/or one sulphur atom; a straight-chain or branched (C_{1-5})alkoxy radical or a (C_{6-10})aryl-(C_{1-5})alkoxy radical or a group of formula $R_{15}O(CH_2CH_2O)_n(CH_2)_m-$, wherein R_{15} signifies a straight-chain or branched (C_{1-5})alkyl radical, n is a whole number from 1 to 20 and m is a whole number from 1 to 5,

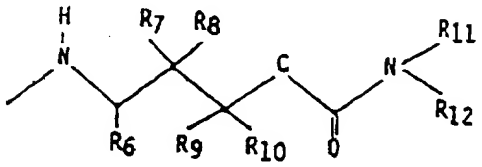
R_1 and R_4 independently signify hydrophilic or hydrophobic side chains,

R_2 signifies a hydroxyl or an amino group, and

R_3 signifies hydrogen, or

R_2 and R_3 together denote an oxo group,

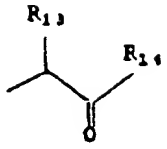
B signifies either a group of formula,



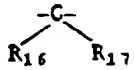
wherein R_6 has the same siognificance as R_1 and R_7 and R_8 have the same significances as R_2 and R_3,

R_9 and R_{10}, independently of one another, respectively signify hydrogen or fluorine,

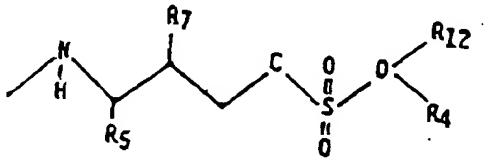
R_{11} and R_{12} are the same or different and respectively signify hydrogen, a straight-chain or branched (C_{1-5})alkyl radical, a (C_{6-10})aryl-(C_{1-5})alkyl or a heteroaryl-(C_{1-5})alkyl radical, in which the heteroaryl moiety is 5- or 6-membered and contains one or two nitrogen atoms, oxygen or sulphur atoms or one nitrogen atom and one oxygen atom and/or one sulphur atom,

or they signify a group of formula 

wherein R_{13} signifies a straight-chain or branched (C_{1-5})alkyl radical or a straight-chain or branched (C_{1-5})hydroxyalkyl radical, R_{14} signifies a hydroxyl radical, a straight-chain or branched (C_{1-5})alkoxy group, an amino or a (C_{1-5})alkylamino group, whereby the alkyl radical is straight-chain or branched, an aminomethylpyridyl group or a benzyl group,

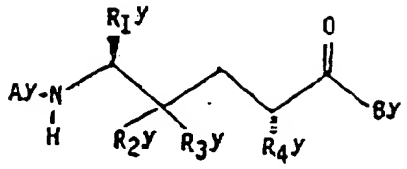
C signifies a bond, or denotes -O-,  or  wherein R_{16} and R_{17}, independently of one another, denote hydrogen or fluorine, or they have the significance given for R_4, or

B signifies a group of formula,



wherein R_4, R_5, R_7 and R_{12} possess the above-mentioned significances and D is -N- or -CH-.

2. A compound according to claim 1 of formula I^Y



I^Y

wherein

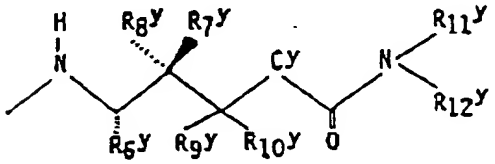
A^Y signifies benzyloxycarbonyl, tert. butoxycarbonyl, pivaloyl, benzoyl or adamantylcarbonyl,

$R_1{}^Y$ signifies cyclohexylmethyl, phenylmethyl, isobutyl and

$R_2{}^Y$ and $R_3{}^Y$ together signify the oxo group, or $R_2{}^Y$ signifies hydrogen and $R_3{}^Y$ signifies hydroxyl,

$R_4{}^Y$ signifies phenylmethyl, n-butyl, isobutyl, isopropyl, pyridylmethyl, 2-butenyl or methylthiomethyl,

B^Y signifies a group of formula,

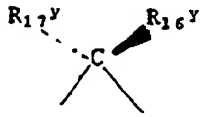


wherein $R_6{}^Y$ is isobutyl, benzyl or cyclohexylmethyl, and either

R_7^Y signifies a hydroxyl radical and R_8^Y signifies hydrogen, if R_9^Y and R_{10}^Y respectively denote hydrogen, or

R_7^Y and R_8^Y together signify the oxo group, if R_9^Y and R_{10}^Y respectively denote fluorine.

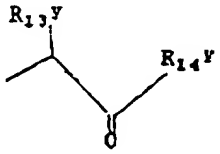
C^Y signifies a bond or a group of formula



wherein R_{16}^Y and R_{17}^Y are fluorine, or R_{16}^Y has the significance of R_4^Y and R_{17}^Y signifies hydrogen,

R_{11}^Y signifies hydrogen or methyl,

R_{12}^Y signifies hydrogen, methyl, i-propyl, i-butyl, 2-butyl or a group of formula



wherein R_{13}^Y is i-butyl and R_{14}^Y is aminomethylpyridyl.

3. Compounds of claims 1 and 2 selected from

(3R,4S,7R,10S)-5-aza-7-(E-2-butenyl)-10-tert.-butyloxycarbonylamino-11-cyclohexyl-4-cyclohexylmethyl-2,2-difluoro-3-hydroxy-6,9-dioxo-undecanoic acid-isobutylamide.

(4S,7R,10S)-5-aza-7-(E-2-butenyl)-10-tert.-butyloxycarbonylamino-11-cyclohexyl-4-cyclohexylmethyl-2,2-difluoro-3,6,9-trioxo-undecanoic acid-isobutylamide.

(3R,4S,7R,10S)-5-aza-7-butyl-10-tert.-butyloxycarbonylamino-11-cyclohexyl-4-cyclohexyl-2,2-difluoro-3-hydroxy-6,9-dioxo-undecanoic acid-isobutylamide.

(2S,6R,7S,10R,13S)-3,8-diaza-2,10-diisobutyl-13-tert.-butyloxycarbonylamino-7-cyclohexylmethyl-5,5-difluoro-6-hydroxy-15-methyl-4,9,12-trioxo-palmitic acid-2-picolylamide.

(2R,4S,5S,8R,11S)-6-aza-2,8-dibenzyl-11-tert.-butyloxycarbonylamino-12-cyclohexyl-5-cyclohexylmethyl-4-hydroxy-7,10-dioxo-lauric acid-butylamide.

(2R,4S,5S,8R,11S)-6-aza-2,8-di(2-butenyl)-11-tert.-butyloxycarbonylamino-12-cyclohexyl-5-cyclohexylmethyl-4-hydroxy-7,10-dioxolauric acid-butylamide.

(2R,4S,5S,8R,11S)-6-aza-2,8-dibutyl-11-tert.-butyloxycarbonylamino-12-cyclohexyl-5-cyclohexylmethyl-4-hydroxy-7,10-dioxo-lauric acid-butylamide.

(2R,4S,5S,8R,10RS,11S)-6-aza-2,8-di(2-butenyl)-11-tert.-butyloxycarbonylamino-12-cyclohexyl-5-cyclohexylmethyl-4,10-dihydro-7-oxo-lauric acid-butylamide.

(2R,4S,5S,8R,11S)-6-aza-11-benzyloxycarbonylamino-2,8-di(2-butenyl)-12-cyclohexyl-5-cyclohexylmethyl-4-hydroxy-7,10-dioxo-lauric acid-butylamide.

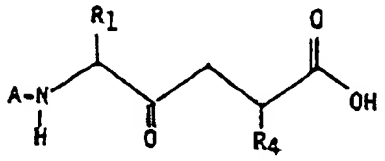
(2S,7S,10R,13S)-3,8-diaza-2,10-diisobutyl-13-tert.-butyloxy-carbonylamino-7-cyclohexylmethyl-5,5-difluoro-15-methyl-4,6,9,12-tetraoxo-palmitic acid-2-picolylamide.

(2S,5R,7S,8S,11R,14S)-3,9-diaza-5,11-di(E-2-butenyl)-14-tert.-butyloxycarbonylamino-8,14-di(cyclohexylmethyl)-7-hydroxy-2-isobutyl-4,10,13-trioxo-tetradecanoic acid-2-picolylamide.

(2R,4S,5S,8R,11S)-6-aza-8-(2E-butenyl)-11-tert.-butyloxycarbonylamino-12-cyclohexyl-5-cyclohexylmethyl-4-hydroxy-2-methyl-7,10-dioxo-lauric acid-butylamide.

4. Process for the production of compounds of formula I, characterised in that

a) a compound of formula II,



II

wherein A, R_1 and R_4 are defined above
is reacted with a compound of formula H-B.
wherein B is defined above

b) a compound of formula I, in which R_7 = OH and R_8 = H, is oxidised to form a compound of formula I, in which R_7 and R_8 together form an oxo group,

c) a compound of formula I, in which R_2 and R_3 together form an oxo group, is reduced to form a compound of formula I, in which R_2 = OH and R_3 = H,

d) a multiple bond found in side chains R_4. R_{16} or R_{17} is reduced, or

e) the protecting group is cleaved from a compound of formula I, in which A is t-BOC, and the free amine is acylated again.

5. A compound according to anyone of claims 1 to 3 for use as a medicament.

6. A compound according to anyone of claims 1 to 3 for use as a renin inhibitor.

7. A compound according to anyone of claims 1 to 3 for use against hypertension or cardiac insufficiency.

8. Pharmaceutical composition containing compounds of anyone of claims 1 to 3 in pharmaceutically acceptable form in association with a pharmaceutical carrier or diluent.

9. Use of the pharmaceutical composition according to claim 6 for the preparation of medicaments for the treatment of hypertension or congestive heart failure.

10. Use of the pharmaceutical composition according to claim 6 for the preparation of medicaments for the treatment of diseases caused by retroviruses.

11. A compound of anyone of claims 1 to 3 for use as a pharmaceutical.

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wherein

A is a N-protected amino acid radical, such as BOC-proline or a peptide, or it signifies an acyl group of formula 

wherein R_5 denotes a straight-chain or branched (C_{1-10})alkyl radical which may be optionally substituted by (C_{1-5})alkoxy or (C_{6-10})aryloxy; a (C_{3-10})cycloalkyl radical, a (C_{3-10})cycloalkyl-(C_{1-5})alkyl radical, a (C_{6-10})aryl radical, a 5- or 6-membered heteroaryl radical containing one or two nitrogen atoms, oxygen or sulphur atoms or one nitrogen atom and one oxygen atom and/or one sulphur atom, or a heteroaryl-(C_{1-5})alkyl radical in which the heteroaryl moiety is 5- or 6-membered and contains one or two nitrogen atoms, oxygen or sulphur atoms or one nitrogen atom and one oxygen atom and/or one sulphur atom; a straight-chain or branched (C_{1-5})alkoxy radical or a (C_{6-10})aryl-(C_{1-5})alkoxy radical or a group of formula $R_{15}O(CH_2CH_2O)_n(CH_2)_m$-, wherein R_{15} signifies a straight-chain or branched (C_{1-5})alkyl radical, n is a whole number from 1 to 20 and m is a whole number from 1 to 5,

R_1 and R_4 independently signify hydrophilic or hydrophobic side chains,

R_2 signifies a hydroxyl or an amino group, and

R_3 signifies hydrogen, or

R_2 and R_3 together denote an oxo group,